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WITNESS my hand this
Ninth day of April 2003

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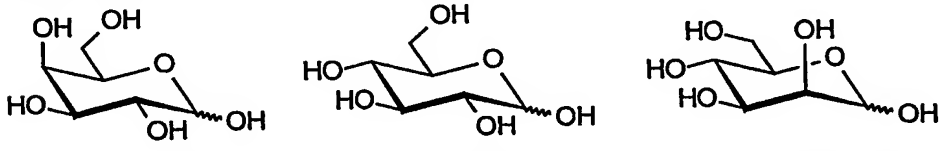
ANOMERIC DERIVATIVES OF MONOSACCHARIDES

FIELD OF THE INVENTION

This invention relates to new compounds and methods for the preparation of combinatorial libraries of potentially biologically active monosaccharide compounds. These compounds are variously functionalised, with a view to varying lipid solubility, size, function and other properties, with the particular aim of discovering novel drug or drug-like compounds, or compounds with useful properties. The invention can provide intermediates, processes and synthetic strategies for the solution or solid phase synthesis of monosaccharides, variously functionalised about the sugar ring, including the addition of aromaticity and charge, and the placement of amino acid and peptide side chain units or isosteres thereof.

BACKGROUND ART

From a drug discovery perspective, carbohydrate pyranose and furanose rings and their derivatives are well suited as templates. Each sugar represents a three-dimensional scaffold to which a variety of substituents can be attached, usually *via* a scaffold hydroxyl group, although occasionally a scaffold carboxyl or amino group may be present for substitution. By varying the substituents, their relative position on the sugar scaffold, and the type of sugar to which the substituents are coupled, numerous highly diverse structures are obtainable. An important feature to note with carbohydrates, is that molecular diversity is achieved not only in the type of substituents, but also in the three dimensional presentation. The different stereoisomers of carbohydrates that occur naturally (examples include glucose, galactose, mannose etc, **Fig 1**), offer the inherent structural advantage of providing alternative presentation of substituents.



Δ E D-Galactose Δ E D-Glucose Δ E D-Mannose

Fig. 1

The first example of a combinatorial approach employing carbohydrate chemistry was a symposium report on the design and synthesis

of a peptidomimetic using a glucose scaffold in the early 1990's[i]. The results revealed that the glucose based structures designed as mimetics of a potent somatostatin (SRIF) agonist acted as agonists at low concentration and, at high concentration, became the first known antagonists of SRIF. Although hardly the production of a library, the results were unique.

Continuing in part the work commenced in the early 1990's, Nicolaou and co-workers began developing carbohydrate based peptido-mimetics targeting integrins. Many integrins recognize an Arg-Gly-Asp (RGD) sequence in ligands such as fibronectin, vitronectin and fibrinogen, each binding with different affinities to the individual integrin receptors. Through a process of rational design a number of carbohydrate based RGD mimetics were synthesized. The chemical synthesis of nine different compounds by this group with very few common intermediates required a considerable amount of chemical effort. It was evident from such results, that in order to generate a number of different structures in a facile manner new chemistries needed to be developed to streamline and enable what at this stage was unfortunately a protracted and arduous methodology.

Since 1998 researchers in the group of Kunz[ii] have been developing a number of carbohydrate building blocks with a similar purpose in mind. In general the building blocks that they have developed are coupled to a solid support to effect the desired chemical transformations. The chemistry developed can be employed to achieve, like the work of Hirschmann and co-workers[iii], the introduction of peptidomimetic side chains to carbohydrate scaffolds in an effort to produce glyco-based mimetics of cyclic peptides. Admittedly, with the chemistry they have developed, there are inherent limitations in the types of functional groups that they are able to introduce and the range of stereoisomeric building blocks that they are able to employ.

Many of the traditional methods of carbohydrate synthesis have proved to be unsuitable to a combinatorial approach, particularly because modern high-throughput synthetic systems require that procedures to be readily automatable.

It is now becoming reasonably established in the art that relates to the solid phase production of combinatorial carbohydrate based libraries, that one

of five protecting groups on a carbohydrate scaffold is a protecting group modified as a linker, so as to allow coupling of the block to a solid support. The strategy that then follows is simple, remove a protecting group and effect coupling at the freed functionality with a peptidomimetic or other reagent. Remove another protecting group and couple with the next reagent, and so on.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country..

OBJECT OF THE INVENTION

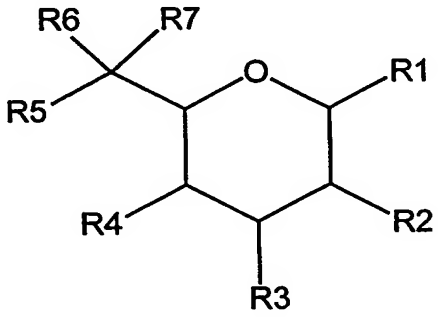
The present invention is directed to a system that allows the chemical synthesis of highly structurally and functionally diverse derivatised carbohydrate and tetrahydropyran structures, of both natural and unnatural origin. The diversity accessible is particularly augmented by the juxtaposition of both structural and functional aspects of the molecules. In order to access a wide range of diverse structures, stereo-center inversion chemistry is required, so as to achieve non-naturally occurring and hard to get sugars in a facile manner. Other chemistries are also required that provide unnatural deoxy or deoxy amino derivative which impart greater structural stability to the drug-like target molecules. With a suite of reagents to effect a suitable range of chemistries on a solid support, allowing such things as; wide functional diversity, highly conserved intermediates, a limited number of common building block to be required, and with suitable chemistry to allow access to unusual carbohydrate stereo-representations and including access to deoxy and deoxy amino analogues, a methodology is then established that can create focused libraries for a known target, or alternatively diversity libraries for unknown targets for random screening.

The compounds and processes described herein are particularly suited to the solid and solution phase combinatorial synthesis of carbohydrate-based libraries, and are amenable to automation. The methods of the invention yield common intermediates that are suitably functionalized to provide diversity in the structure of the compounds so generated. In this way

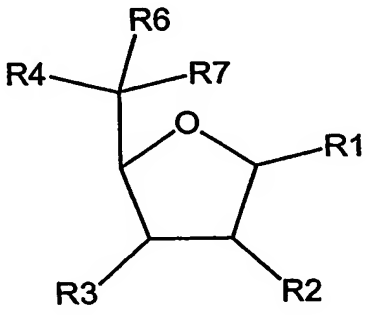
the technology described can produce many and varied compounds around the basic structure shown in Figure 1. Using this method, it is possible to introduce varied functionality in order to modulate both the biological activity and pharmacological properties of the compounds generated.

Thus the compounds and methods disclosed herein provide the ability to produce random or focused combinatorial-type libraries for the discovery of other novel drug or drug-like compounds, or compounds with other useful properties in an industrially practical manner.

In a first aspect, the invention provides a monosaccharide compound of formula I or formula II



formula I



formula II

in which the monosaccharide ring may be of the pyranose or furanose form and may be of any configuration and the anomeric center may be of either the Δ or E configuration;

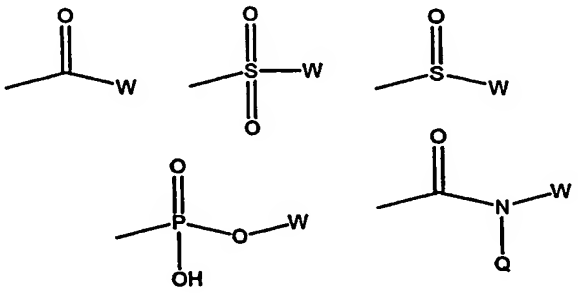
R6 and R7 are hydrogen, or together form a carbonyl oxygen;

R1 may be hydrogen or -P(Z)Y wherein;

P may be a carbon or nitrogen atom;

When P is nitrogen

Y is selected from hydrogen, or the following;



Z is selected from hydrogen or X;

Q is selected from hydrogen or W;

The groups W are independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid;

The groups X are independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, acyl, arylacyl, heteroarylacyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid;

Where P is carbon,

Y is selected from hydrogen, double bond oxygen (=O) to form a carbonyl, or triple bond nitrogen to form a nitrile.

Z may be optionally absent, or is selected from hydrogen or X,

Wherein X is independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, aminoalkyl, aminoaryl, aryloxy, alkoxy, heteroaryloxy, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, acyl, arylacyl, heteroarylacyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl,

heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid;, heteroaryloxy, aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may optionally be further substituted;

It is understood that the rules of molecular stoichiometry will be upheld by the default addition of hydrogens atoms as required.

The groups Z and Y may be combined to form a monocyclic or bicyclic ring structure of 4 to 10 atoms. This ring structure may be further substituted with X groups;

The groups R2, R3, R4 and R5 are independently selected from hydrogen, OH, OX, N(Z)Y, wherein N(Z)Y is as defined above and X is independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, aminoalkyl, aminoaryl, aryloxy, alkoxy, heteroaryloxy, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, acyl, arylacyl, heteroarylacyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid;

A preferred embodiment of the first aspect provides for compounds of formula I in which R1 is H and R4 is N(Z)Y;

In a particularly preferred embodiment R1 is H and R4 is N(Z)Y wherein Z is hydrogen;

A further embodiment of the first aspect provides for compounds of formula I in which R1 is N(Z)Y;

A further embodiment of the first aspect provides for compounds of formula I in which R1 and R4 are independently N(Z)Y;

Another embodiment provides for compounds of formula I in which R1 is H and both R2 and R4 are N(Z)Y;

In a preferred embodiment provides for compounds of formula I in which the ring is of the gluco, galacto or allo configuration;

A further embodiment provides for compounds of formula I in which R1 is N(Z)Y and R2 is N(Z)Y;

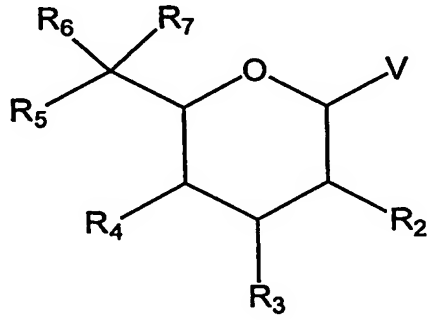
A further embodiment provides for compounds of formula I in which R1 is P(Z)Y, wherein P is carbon and Y is hydrogen.

A further embodiment provides for compounds of formula I in which R1 is P(Z)Y and R2 is N(Z)Y, wherein P is carbon and Y on P is hydrogen.

A further embodiment provides for compounds of formula I in which R1 is P(Z)Y and R4 is N(Z)Y, wherein P is carbon and Y is hydrogen.

A further embodiment provides for compounds of formula II in which R1 is N(Z)Y and R4 is N(Z)Y.

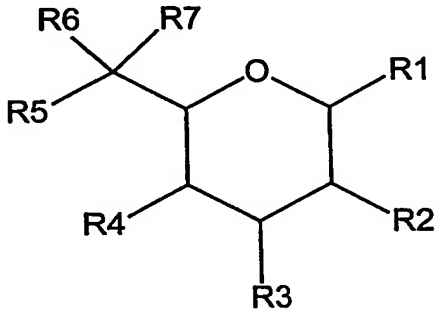
In a second aspect, the invention provides for a method of synthesis of compounds of formula I in which R1 is hydrogen, comprising the step of reducing a synthetic intermediate of formula III, in which the substituent V is either bromine or chlorine, R6 and R7 are as defined in the first aspect, R5, R4, R3, and R2 are independently selected from OH, O-acyl, N_3, NHDde, NHDTPM, NHZ, NHBOC, phthalimide, O-protecting group or when R6 and R7 together for a carbonyl oxygen, R5 may additionally be optionally substituted O-alkyl, O-arylalkyl or O-aryl. Where the protecting groups may be chosen from any suitable oxygen protecting groups known in the art, including acetals and ketals which protect two adjacent oxygens. The compounds of formula III may also comprise an aspect of the invention.



formula III

In a third aspect, the invention provides for a method of synthesis of compounds of formula I in which R1 is N(Z)Y comprising the step of reacting a compound of formula III with and azide nucleophile, in which the substituents for formula III are as described in the second aspect.

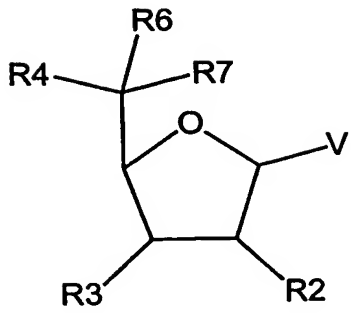
In a fourth aspect, the invention provides for a method of combinatorial synthesis of compounds of the formula I comprising the step of immobilizing a compound of formula IV onto a support. Said support may be soluble or insoluble. Non-limiting examples of insoluble supports include derivatised polystyrene, tentagel, wang resin, MBHA resin, aminomethylpolystyrene, rink amide resin etc. Non-limiting examples of soluble supports include DOX-mpeg, polyethylene glycol etc.



formula IV

Wherein R1 is as defined in the first aspect, R2, R3, R4, R5, R6 and R7 are as defined in the second aspect, and the linkage between the compound of formula IV and the support is through any of positions R2, R3,R4 or R5.

In a fifth aspect, the invention provides for a method of synthesis of compounds of formula II in which R1 is N(Z)Y, comprising the step of reacting a compound of formula V in the presence of a lewis acid with an azide source.

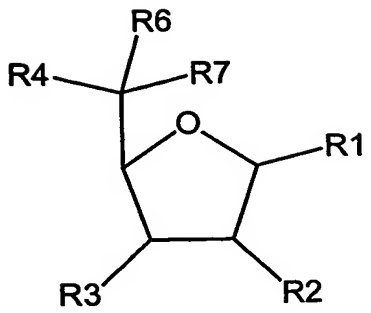


formula V

in which the substituent V is -OAcyl, R6 and R7 are as defined in the first aspect, R4, R3, and R2 are independently selected from OH, O-acyl, N_3, NHDde, NHDTPM, NHZ, NHBOC, phthalimide, O-protecting group or when R6 and R7 together for a carbonyl oxygen, R4 may additionally be optionally substituted O-alkyl, O-arylalkyl or O-aryl. Where the protecting groups may be chosen from any suitable oxygen protecting groups known in the art, including acetals and ketals which protect two adjacent oxygens.

In a sixth aspect, the invention provides for a method of synthesis of compounds of formula II in which R1 is H, comprising the step of reducing a compound of formula V in which the substituents for formula III are as described in the fifth aspect.

In a seventh aspect, the invention provides for a method of combinatorial synthesis of compounds of formula II comprising the step of immobilizing a compound of formula VI onto an support. Said support may be soluble or insoluble. Non-limiting examples of insoluble supports include derivatised polystyrene, tentagel, wang resin, MBHA resin, aminomethylpolystyrene, rink amide resin etc., Non-limiting examples of soluble supports include DOX-mpeg, polyethylene glycol etc.



formula VI

Wherein R1 is as defined in the first aspect, R2, R3, R4, R6 and R7 are as defined in the fifth aspect, and the linkage between the compound of formula VI and the support is through any of positions R2, R3, or R4.

In a eighth aspect, the invention provides for a method of solution phase combinatorial synthesis of compounds of formula I comprising the step of alkylating a free hydroxyl on a compound of formula IV, wherein R1 is as defined in the first aspect, R2, R3, R4, R5, R6 and R7 are as defined in the second aspect and any one of the protecting substituents may be removed prior to alkylation.

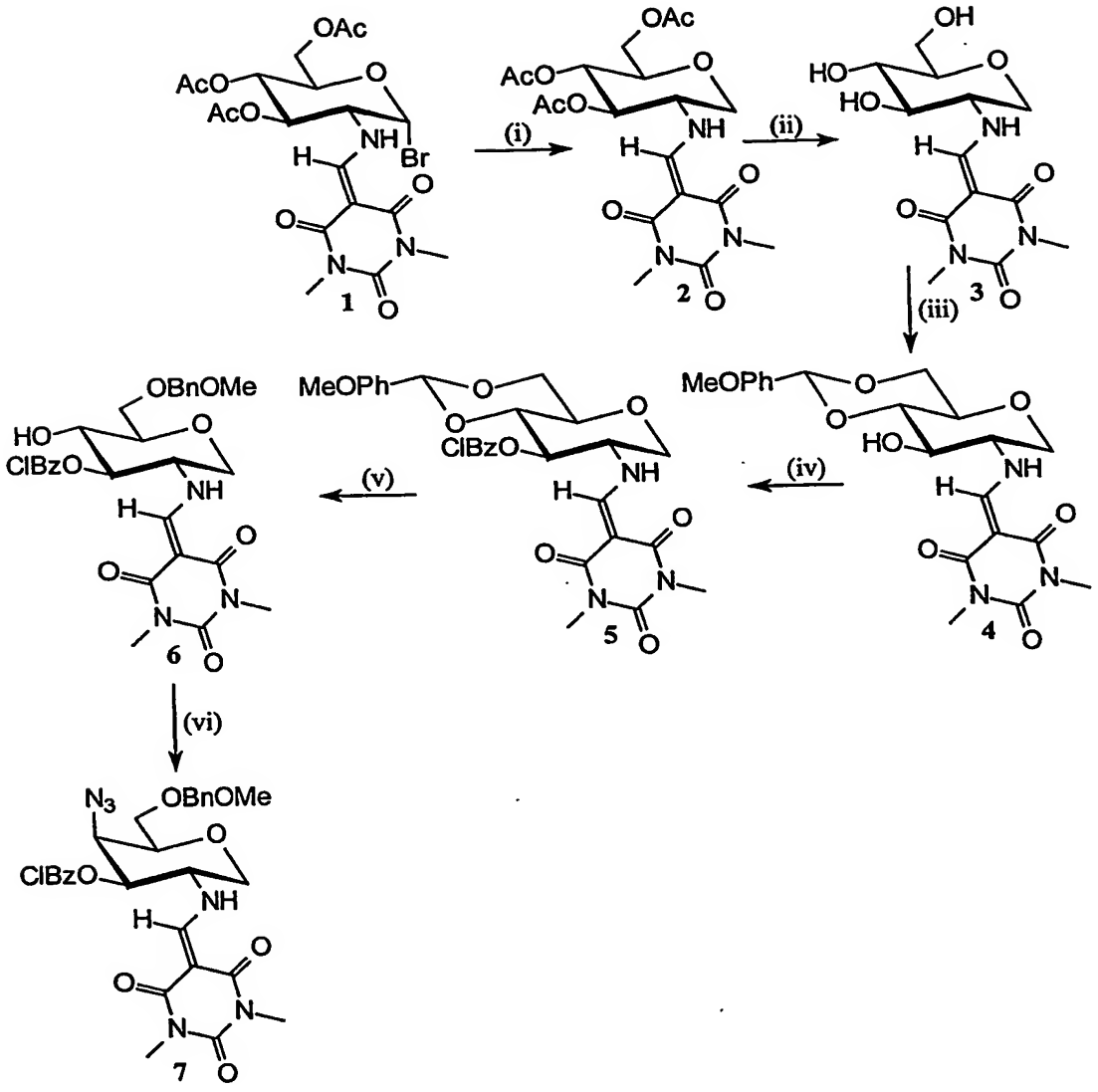
Compounds of the invention are useful in screening for biological activity.

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

BEST MODE

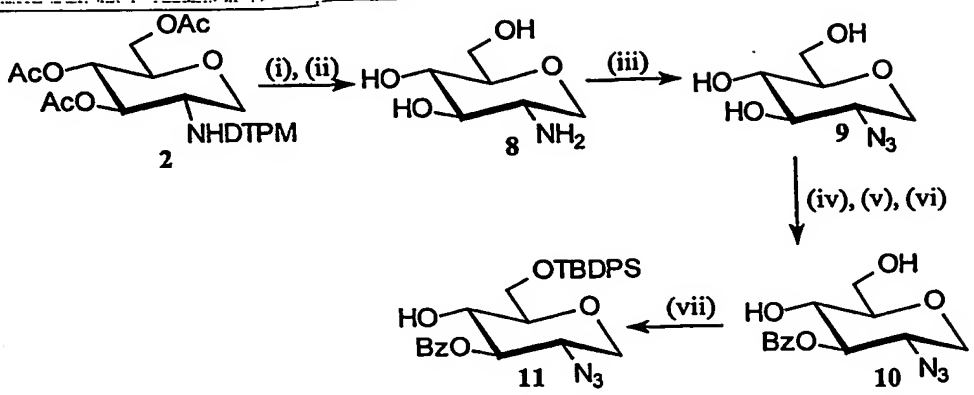
Embodiments of the invention will be described in the examples below.

Example 1: Synthesis of a 2-deoxy-2-NHDTPM-4-Deoxy-4-Azido-D-Galactopyran H-Glycoside



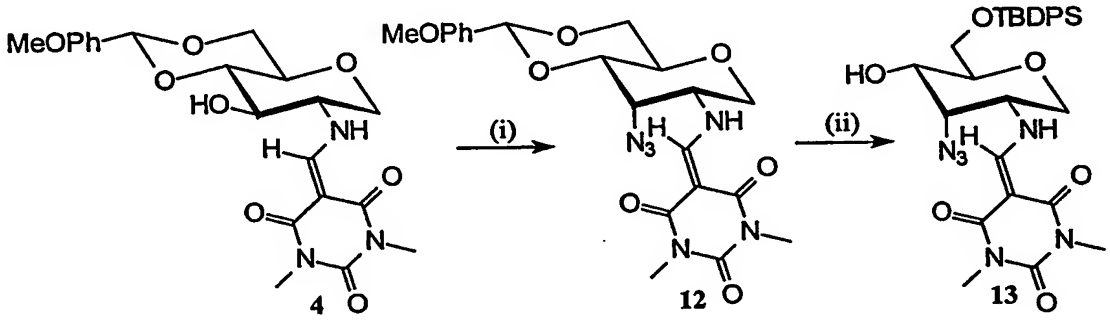
Conditions: (i) Bu_3SnH, toluene, reflux, 2.5hrs, quant.; (ii) NaOMe/MeOH, 2hrs, RT, quant.; (iii) *p*-methoxybenzaldehyde dimethylacetal, *p*-toluenesulphonic acid, DMF, 6hrs, 70°C, 86%; (iv) *p*-chlorobenzoylchloride, pyridine, 1hr, RT, 83%; (v) $NaCNBH_3$, TFA, Mol. sieves 3Å, DMF, 16hrs, 55°C, 93%; (vi) (a) Tf_2O, pyridine, DCM, -20°C, (b) NaN_3, DMF, 1hr, RT, 93%.

Example 2: Synthesis of a Differentially Protected Glucopyran H-Glycoside



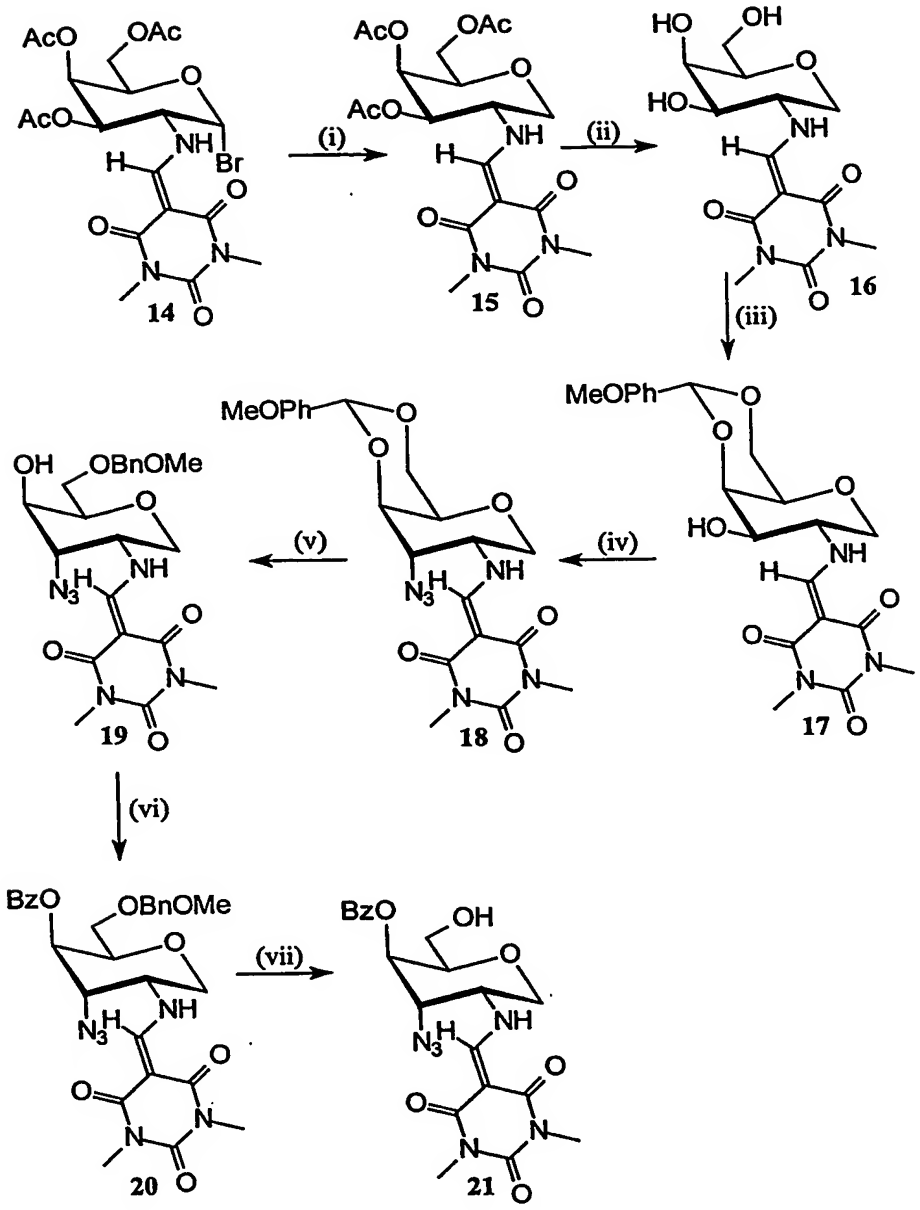
Conditions: (i) NaOMe/MeOH, RT, 2hrs; (ii) hydrazine hydrate, (80-90% over 2 steps); (iii) TfN_3, RT, CH_2Cl_2, MeOH, H_2O/cat. $CuSO_4$, 98%; (iv) C_6H_5-$CH(OMe)_2$, CH_3CN/cat. TsOH, 70°C; (v) BzCl, pyridine, RT' (vi) CH_3CN/MeOH/H_2O, cat. TsOH, 70°C (69% over 3 steps); (vii) TBDPS-Cl, pyridine, 120°C, 87%;

Example 3: Synthesis of a 2-deoxy-2-NHDTPM-3-Deoxy-3-Azido-D-Allopyran H-Glycoside



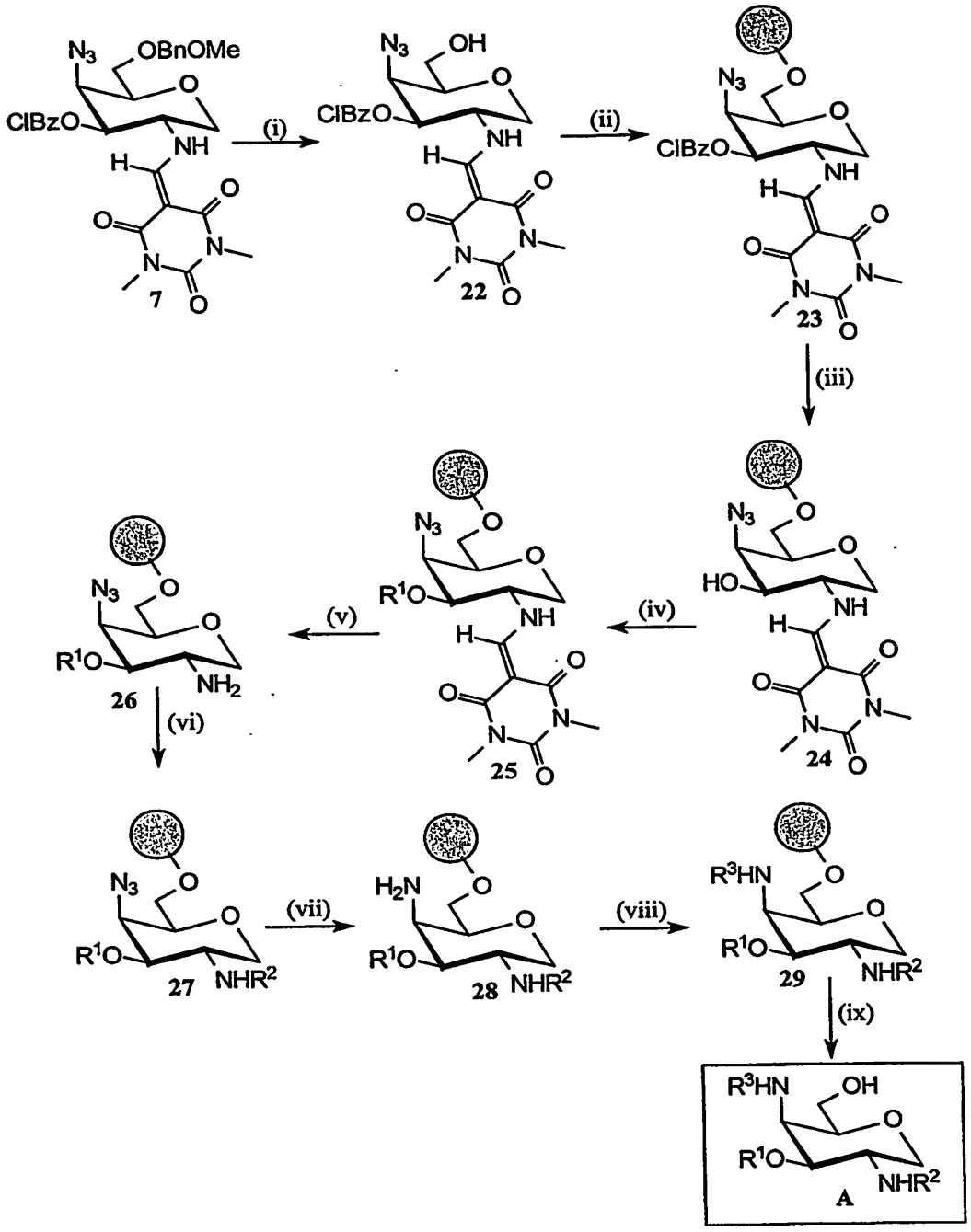
Conditions: (i) Tf_2O, pyridine, DCM, -20°C, (b) NaN_3, DMF, 1hr, RT; (ii) (a) TsOH, MeOH, MeCN, H_2O, TBDPS-Cl, 1,2-DCE, Imidazole.

Example 4: Synthesis of a 2-deoxy-2-NHDTPM-3-Deoxy-3-Azido-Gulopyran H-Glycoside



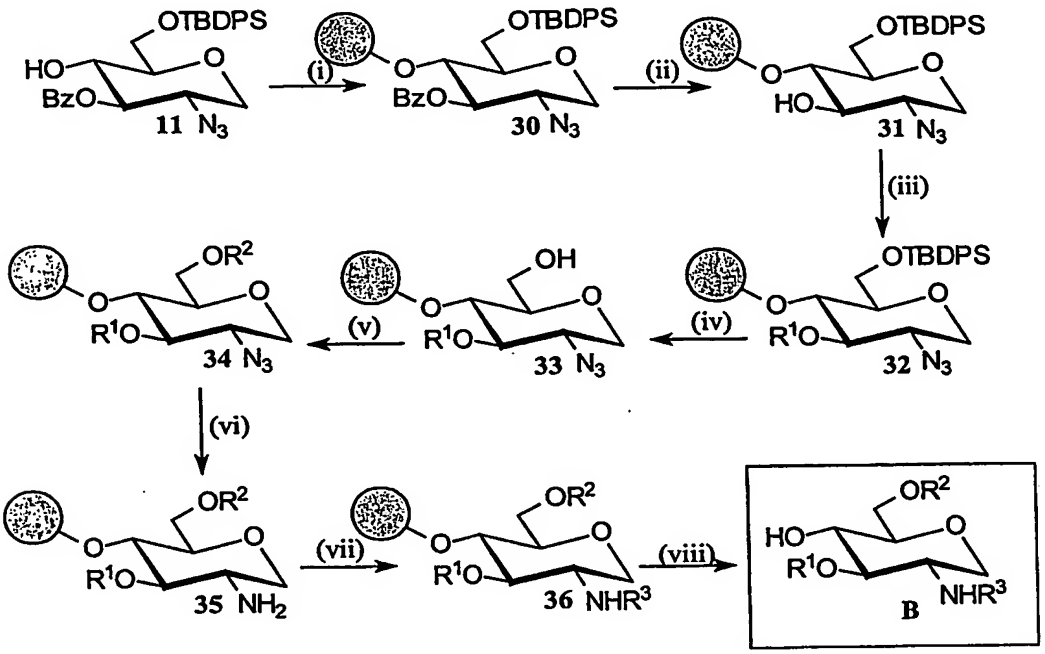
Conditions: (i) Bu_3SnH, toluene, reflux, 2.5hrs, quant.; (ii) NaOMe/MeOH, RT, 2hrs; (iii)) *p*-methoxybenzaldehyde dimethylacetal, *p*-toluenesulphonic acid, DMF, 6hrs, 70^{0}C; (iv) Tf_2O, pyridine, DCM, -20^{0}C, (b) NaN_3, DMF, 1hr, RT; (v) $NaCNBH_3$, TFA, Mol. sieves 3Å, DMF, 15-20hrs.

Example 5: Synthesis of a Library of Compound by Solid Phase Techniques Using Building Block **7**



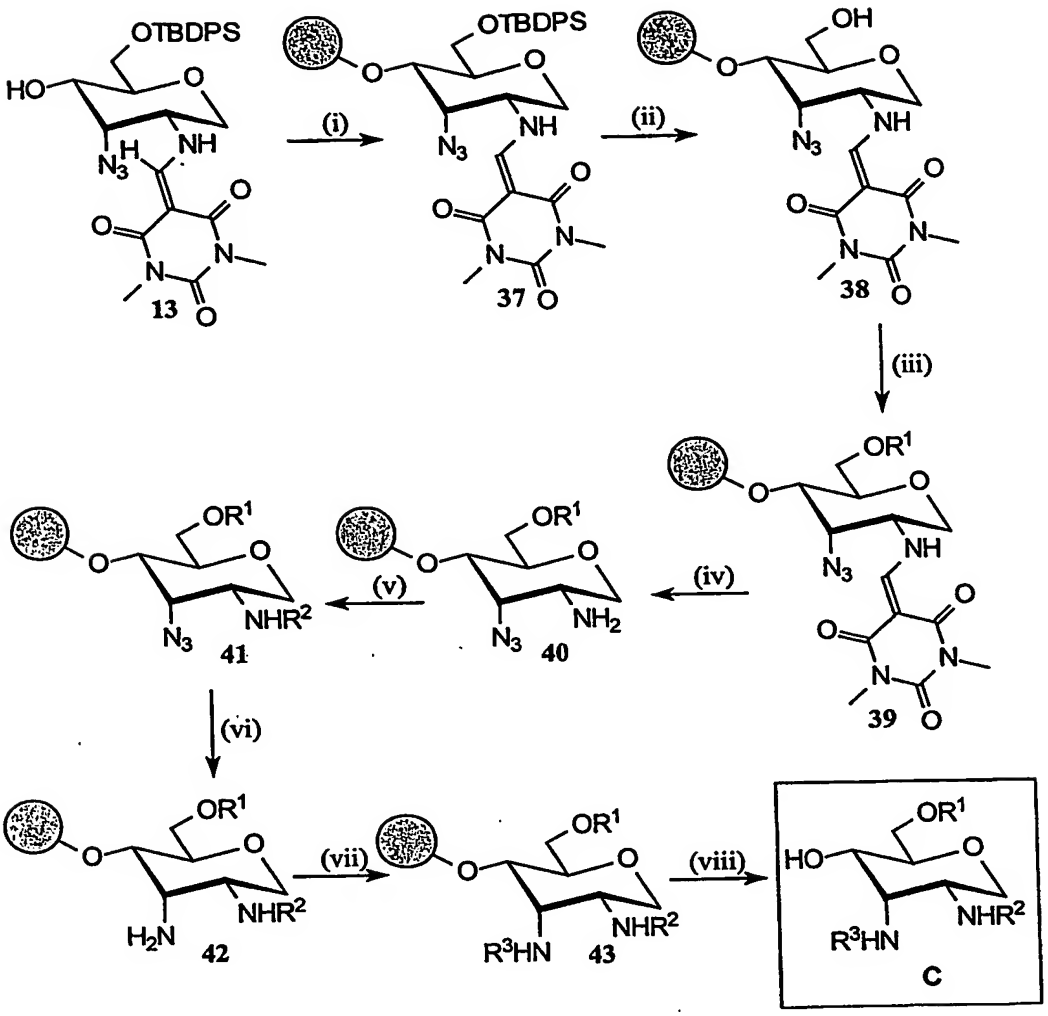
Conditions: (i) DDQ, (ii) Trichloroacetimidate derivatised-acid labile linker-resin conjugate, borontrifluoroetherate, DCM; (iii) NaOMe/MeOH/THF; (iv) aminoacid mimetic-halide (either aryl or alkyl halide), base; (v) hydrazine hydrate, DMF; (vi) amino acid mimetic derivatised as an anhydride, carboxylate or acid chloride, and base or activating reagent; (vii) DTT; (viii) amino acid mimetic derivatised as an anhydride, carboxylate or acid chloride, and base or activating reagent; (ix) TFA.

*Example 6: Synthesis of a Library of Compound by Solid Phase Techniques Using Building Block **11***



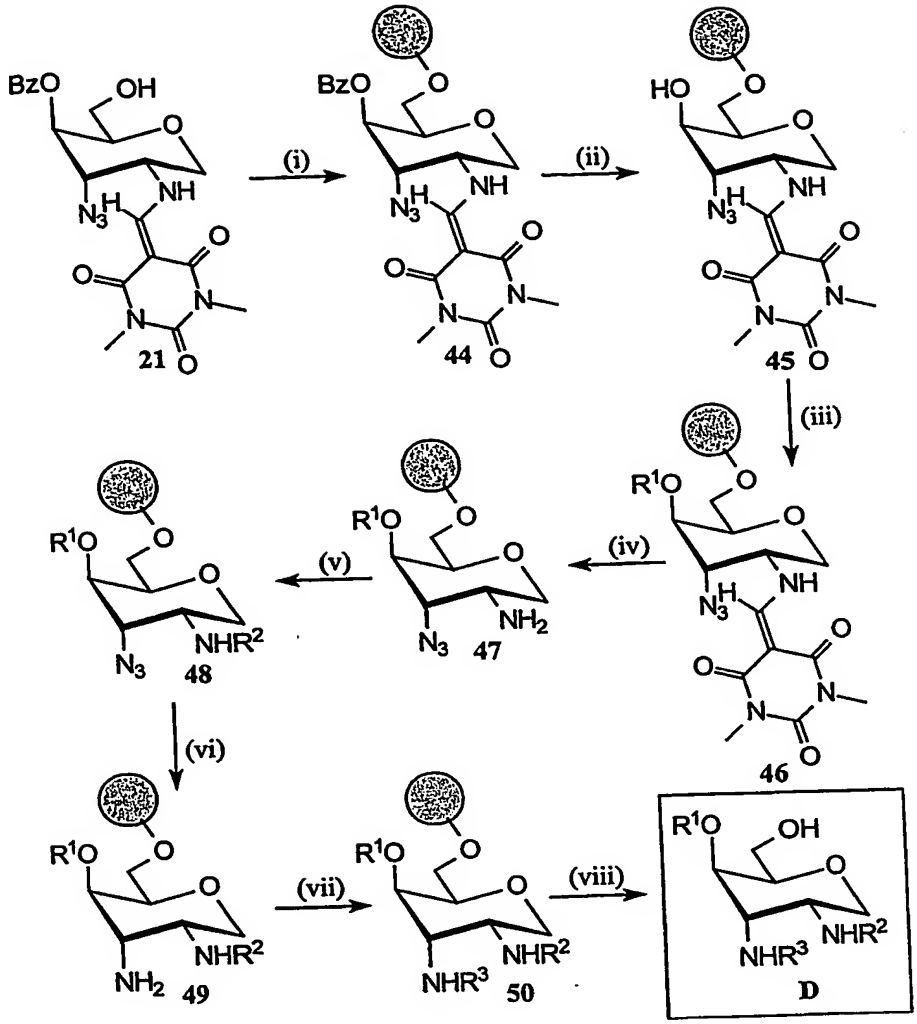
Conditions: (i) Trichloroacetimidate derivatised acid labile linker-resin conjugate, $BF_3.Et_2O$; (ii) NaOMe/MeOH; (iii) aminoacid mimetic-halide (either aryl or alkyl halide), base; (iv) TBAF/THF; (v) aminoacid mimetic-halide (either aryl or alkyl halide), base; (vi) DTT; (vii)) amino acid mimetic derivatised as an anhydride, carboxylate or acid chloride, and base or activating reagent; (viii) TFA.

*Example 7: Synthesis of a Library of Compound by Solid Phase Techniques Using Building Block **13***



Conditions: (i) Trichloroacetimidate derivatised acid labile linker-resin conjugate, $BF_3.Et_2O$; (ii) TBAF/THF; (iii) aminoacid mimetic-halide (either aryl or alkyl halide), base; (iv) hydrazine hydrate, DMF; (v) amino acid mimetic derivatised as an anhydride, carboxylate or acid chloride, and base or activating reagent; (vi) DTT; (vii) amino acid mimetic derivatised as an anhydride, carboxylate or acid chloride, and base or activating reagent; (viii) hΘ

*Example 8: Synthesis of a Library of Compound by Solid Phase Techniques Using Building Block **21***



Conditions: (i) Trichloroacetimidate derivatised acid labile linker-resin conjugate, $BF_3.Et_2O$; (ii) NaOMe/MeOH; (iii) aminoacid mimetic-halide (either aryl or alkyl halide), base; (iv) hydrazine hydrate, DMF; (v) amino acid mimetic derivatised as an anhydride, carboxylate or acid chloride, and base or activating reagent; (vi) DTT; (vii) amino acid mimetic derivatised as an anhydride, carboxylate or acid chloride, and base or activating reagent; (viii) TFA.

Example 9: Synthesis of an Exemplary Library 1

In this example three different mimetics of three different peptide residues (ie. Phe mimetic 1, 2 and 3, Lys mimetic 1, 2 and 3, and Trp mimetic 1, 2 and 3[§])

maintain their position on the scaffold (Phe=R^1, Lys=R^2, Trp=R^3), but the different mimetics are varied in relation to one another. Compounds indicated by "" are also found in the library exemplified in* **Table 2.**

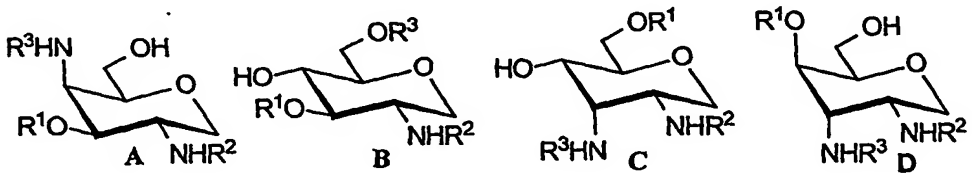


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Table 1

Comp.	R^1	R^2	R^3
51 *	Phe mimetic 1	Lys mimetic 1	Trp mimetic 1
52	Phe mimetic 2	Lys mimetic 1	Trp mimetic 1
53	Phe mimetic 3	Lys mimetic 1	Trp mimetic 1
54	Phe mimetic 1	Lys mimetic 1	Trp mimetic 2
55 *	Phe mimetic 2	Lys mimetic 1	Trp mimetic 2
56	Phe mimetic 3	Lys mimetic 1	Trp mimetic 2
57	Phe mimetic 1	Lys mimetic 1	Trp mimetic 3
58	Phe mimetic 2	Lys mimetic 1	Trp mimetic 3
59 *	Phe mimetic 3	Lys mimetic 1	Trp mimetic 3
60 *	Phe mimetic 1	Lys mimetic 2	Trp mimetic 1
61	Phe mimetic 2	Lys mimetic 2	Trp mimetic 1
62	Phe mimetic 3	Lys mimetic 2	Trp mimetic 1
63	Phe mimetic 1	Lys mimetic 2	Trp mimetic 2
64 *	Phe mimetic 2	Lys mimetic 2	Trp mimetic 2
65	Phe mimetic 3	Lys mimetic 2	Trp mimetic 2
66	Phe mimetic 1	Lys mimetic 2	Trp mimetic 3
67	Phe mimetic 2	Lys mimetic 2	Trp mimetic 3
68 *	Phe mimetic 3	Lys mimetic 2	Trp mimetic 3
69 *	Phe mimetic 1	Lys mimetic 3	Trp mimetic 1
70	Phe mimetic 2	Lys mimetic 3	Trp mimetic 1
71	Phe mimetic 3	Lys mimetic 3	Trp mimetic 1
72	Phe mimetic 1	Lys mimetic 3	Trp mimetic 2
73 *	Phe mimetic 2	Lys mimetic 3	Trp mimetic 2
74	Phe mimetic 3	Lys mimetic 3	Trp mimetic 2
75	Phe mimetic 1	Lys mimetic 3	Trp mimetic 3
76	Phe mimetic 2	Lys mimetic 3	Trp mimetic 3
77 *	Phe mimetic 3	Lys mimetic 3	Trp mimetic 3

Example 10: Synthesis of an Exemplary Library 2

In this example three different mimetics of three different peptide residues (ie. Phe mimetic 1, 2 and 3, Lys mimetic 1, 2 and 3, and Trp mimetic 1, 2 and 3[§]) are varied in their substitution point around the scaffold, ie. Phe mimetic 1 moves from R^1 to R^2 to R^3, and so on.

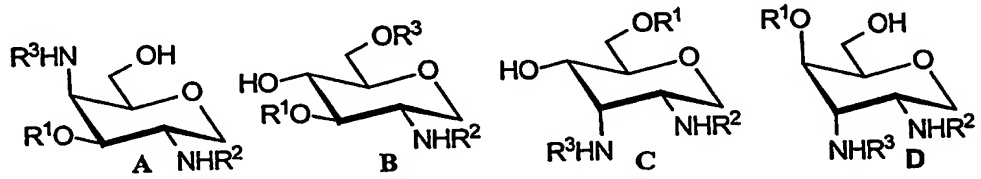


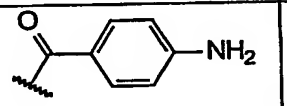
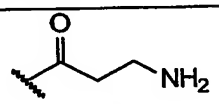
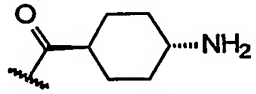
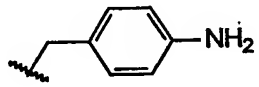
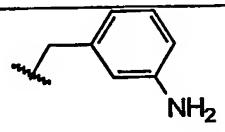
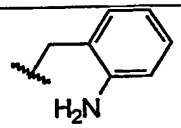
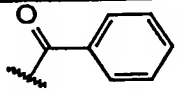
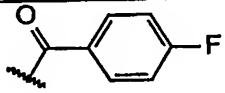
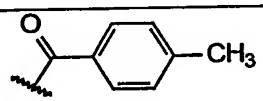
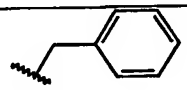
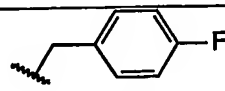
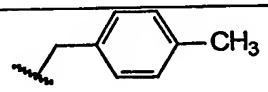
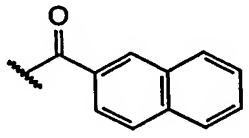
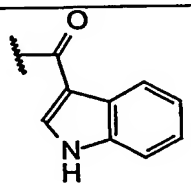
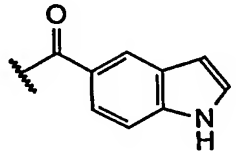
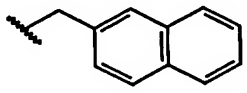
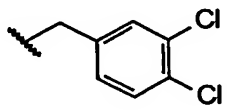
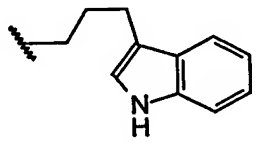
Table 2

Comp.	R^1	R^2	R^3
51	Phe mimetic 1	Lys mimetic 1	Trp mimetic 1
78	Lys mimetic 1	Trp mimetic 1	Phe mimetic 1
79	Trp mimetic 1	Phe mimetic 1	Lys mimetic 1
60	Phe mimetic 1	Lys mimetic 2	Trp mimetic 1
80	Lys mimetic 2	Trp mimetic 1	Phe mimetic 1
81	Trp mimetic 1	Phe mimetic 1	Lys mimetic 2
69	Phe mimetic 1	Lys mimetic 3	Trp mimetic 1
82	Lys mimetic 3	Trp mimetic 1	Phe mimetic 1
83	Trp mimetic 1	Phe mimetic 1	Lys mimetic 3
55	Phe mimetic 2	Lys mimetic 1	Trp mimetic 2
84	Lys mimetic 1	Trp mimetic 2	Phe mimetic 2
85	Trp mimetic 2	Phe mimetic 2	Lys mimetic 1
64	Phe mimetic 2	Lys mimetic 2	Trp mimetic 2
86	Lys mimetic 2	Trp mimetic 2	Phe mimetic 2
87	Trp mimetic 2	Phe mimetic 2	Lys mimetic 2
73	Phe mimetic 2	Lys mimetic 3	Trp mimetic 2
88	Lys mimetic 3	Trp mimetic 2	Phe mimetic 2
89	Trp mimetic 2	Phe mimetic 2	Lys mimetic 3
59	Phe mimetic 3	Lys mimetic 1	Trp mimetic 3
90	Lys mimetic 1	Trp mimetic 3	Phe mimetic 3

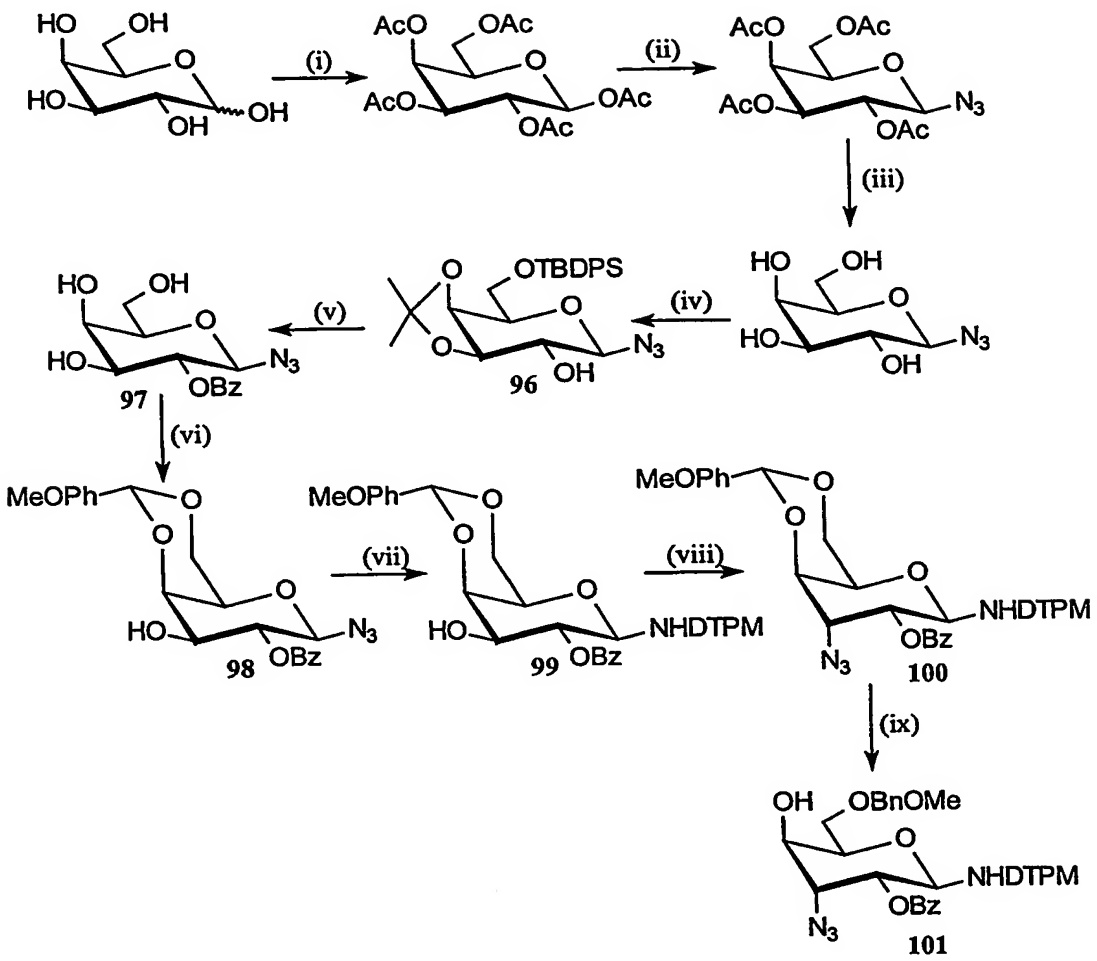
91	Trp mimetic 3	Phe mimetic 3	Lys mimetic 1
68	Phe mimetic 3	Lys mimetic 2	Trp mimetic 3
92	Lys mimetic 2	Trp mimetic 3	Phe mimetic 3
93	Trp mimetic 3	Phe mimetic 2	Lys mimetic 2
77	Phe mimetic 3	Lys mimetic 3	Trp mimetic 3
94	Lys mimetic 3	Trp mimetic 3	Phe mimetic 3
95	Trp mimetic 3	Phe mimetic 3	Lys mimetic 3

§The various scaffold substituents Lys, Phe, and Trp mimetics 1,2 and 3, are listed in **Table 3** below. It is noted that in some case amine protection is required, which is typically effected by Boc protection. It is further noted that in some cases an *O*-linked mimetic is required and in other cases an *N*-linked mimetic is required. In the cases of the *O*-linked Lys mimetics, the mimetic is coupled as either the para, ortho or meta nitrobenzyl derivative and subsequently reduced to the amine.

Table 3

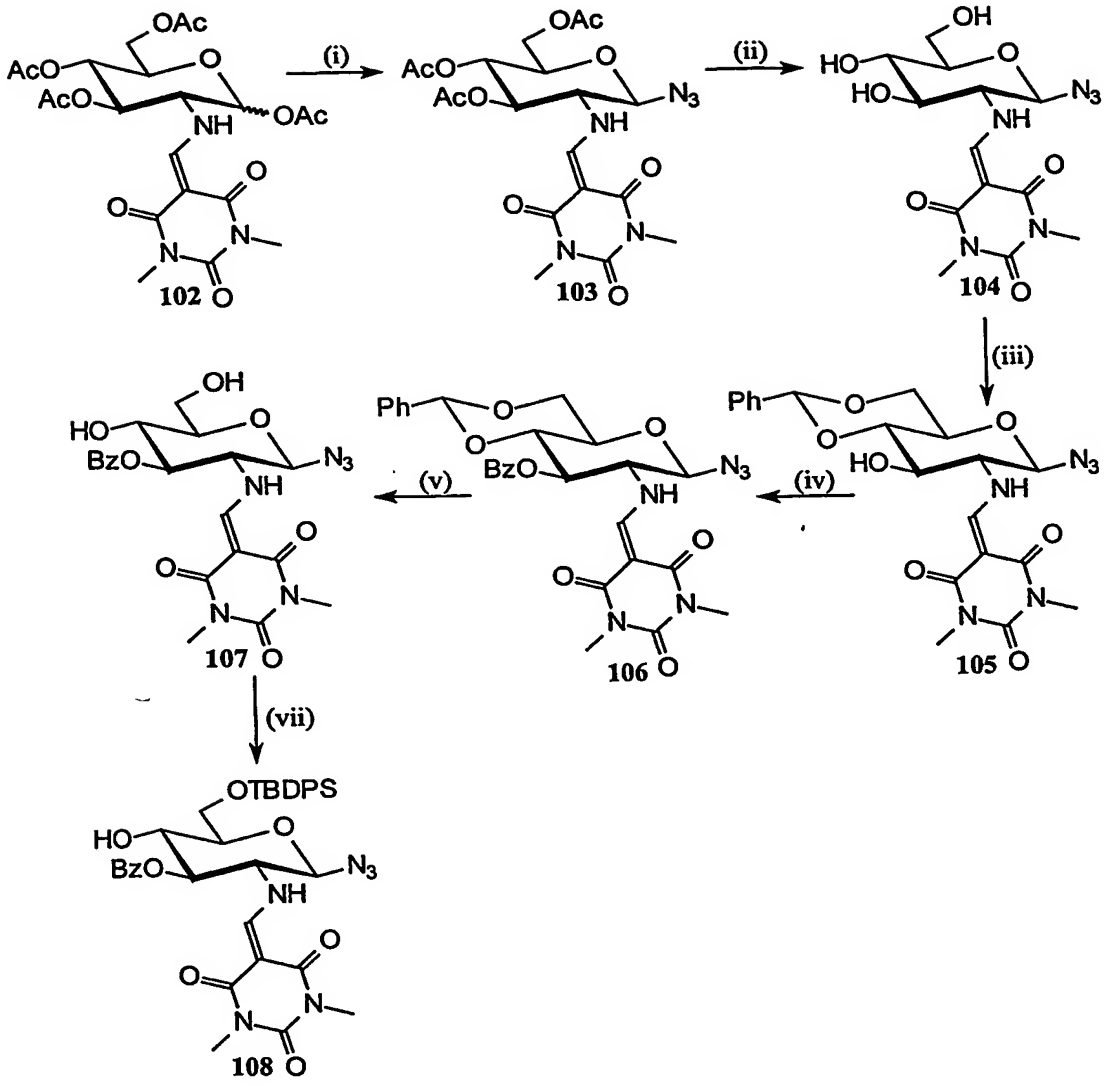
	Mimetic 1	Mimetic 2	Mimetic 3
Lys (*N*-linked)			
Lys (*O*-linked)			
Phe (*N*-linked)			
Phe (*O*-linked)			
Trp (*N*-linked)			
Trp (*O*-linked)			

Example 11: N-glycosides



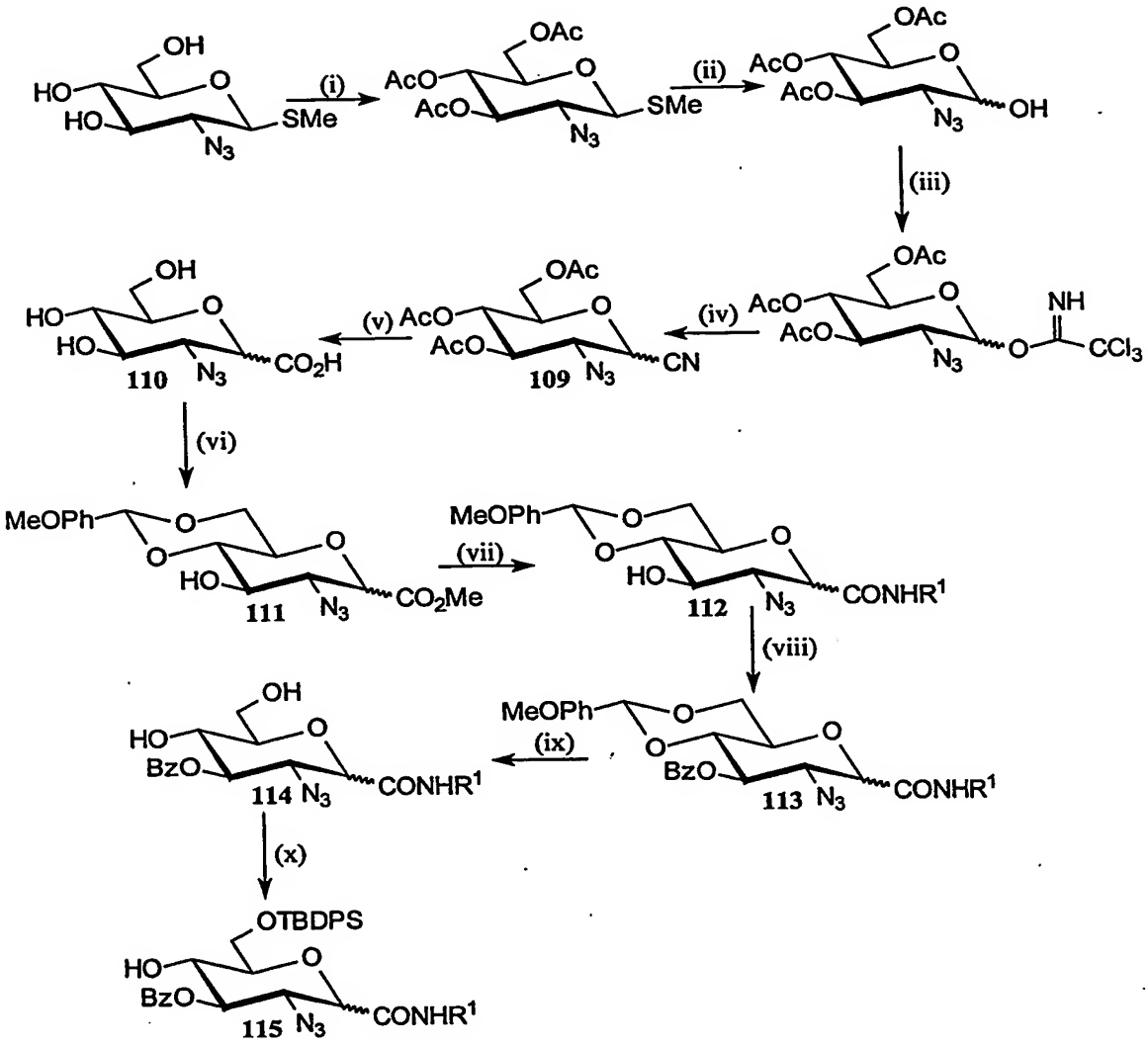
Conditions: (i) Ac_2O, NaOAc; (ii) TMS-N_3, TMS-OTF, DCM; (iii) NaOMe/MeOH, (iv) (a) TBDPS-Cl, 1,2-DCE, imidazole; (b) 2,2-dimethoxy-propane, TsOH, MeCN; (v) (a) Benzoylchloride, pyridine, 1,2-DCE, DMAP; (b) MeOH, TsOH, MeCN,, H_2O (vi) *p*-methoxybenzaldehyde dimethylacetal, TsOH, MeCN; (vii) (a) DTT, (b) DTPM reagent; (viii) (a) Tf_2O, pyridine, DCM, (b) NaN_3, DMF; (ix) $NaCNBH_3$, TFA, Mol. sieves 3Å, DMF.

Example 12: Synthesis of N-Glycoside 2



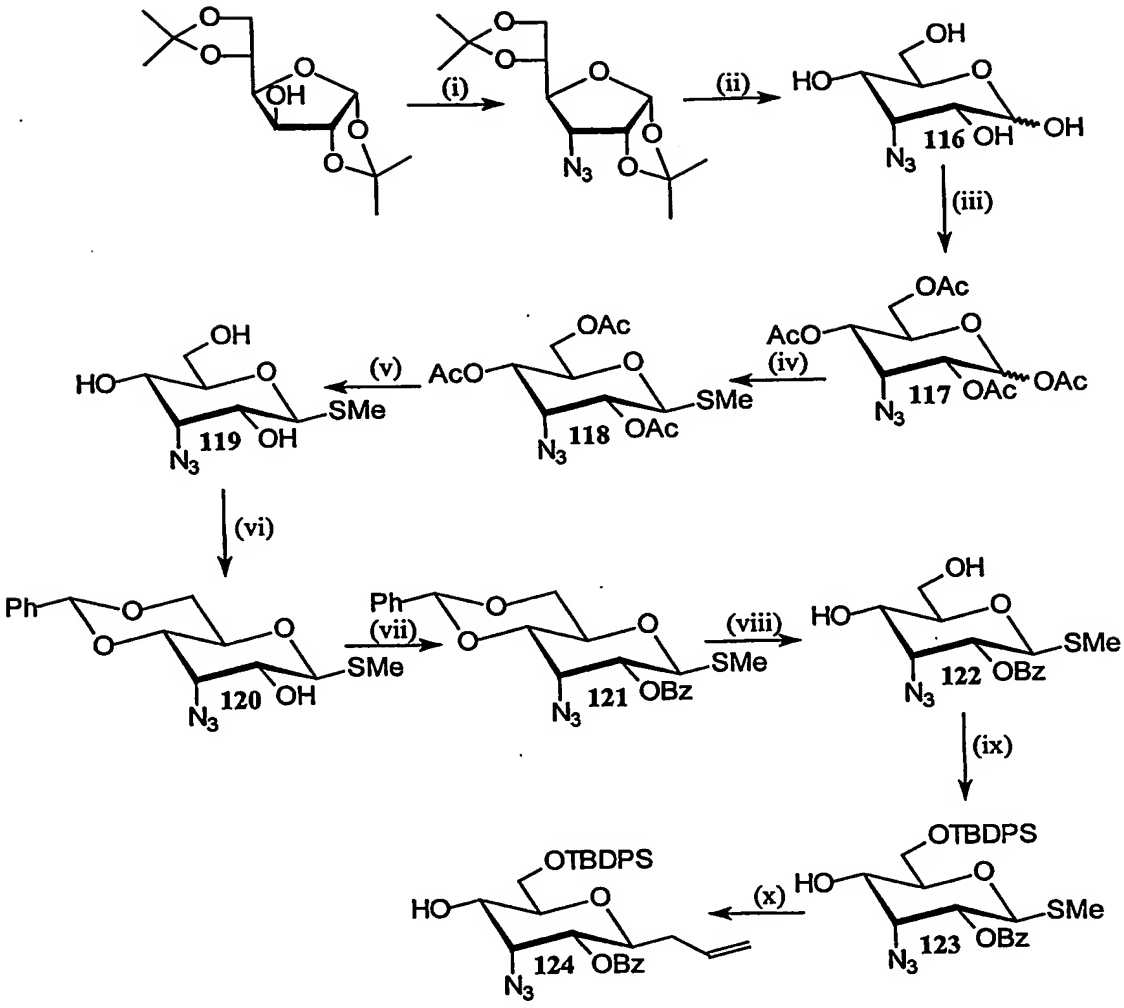
Conditions: (i) TMS-N_3, TMSOTf; (ii) NaOMe/MeOH; (iii) Δ Δ-dimethoxytoluene, TsOH, MeCN; (iv) benzoylchloride, 1,2-DCE, pyridine, DMAP; (v) TsOH, MeCN, MeOH, H_2O; (vii) TBDPS-Cl, 1,2-DCE, imidazole.

Example 13: Synthesis of a Carboxyl C-Glycoside 1



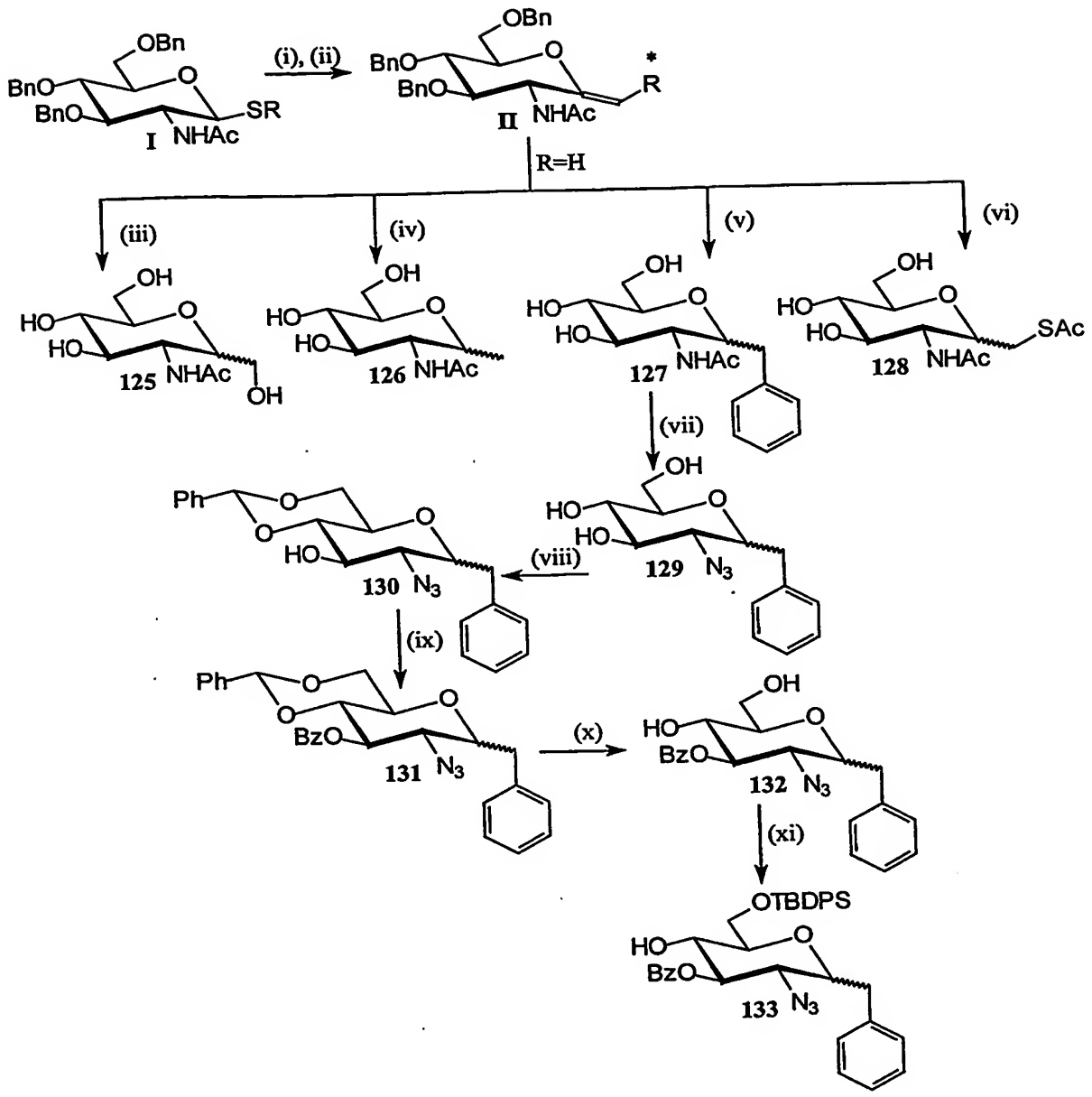
Conditions: NaOMe/MeOH; (ii) Acetone, NBS; (iii) trichloroacetonitrle, potassium carbonate, DCM; (iv) TMS-CN, TMS-Otf, DCM; (v)$NaOH/H_2O_2$; (vi) (a) TMS-CH_2N_2; (b) *p*-methoxybenzaldehyde dimethylacetal, CSA, MeCn, DMF; (vii) (a) LiOH, H_2O, THF; (b) HBTU, DIPEA, DMF, R^1-NH_2; (viii) benzoylchloride, pyridine, 1,2-DCE, DMAP; (TsOH, MeOH, MeCN, H_2O; (x) TBDPS-Cl, imidazole, 1,2-DCE.

Example 14: Synthesis of an Allyl C-Glycoside



Conditions: (i) Tf_2O, pyridine, DCM; (b) NaN_3, DMF; (ii) acetone, H^+; (iii) Ac_2O, pyridine; (iv) hexamethyldisilazane, I_2, CH_3-S-S-CH_3; (v) NaOMe/MeOH; (vi) TsOH, Δ Δ-dimethoxytoluene, MeCN; (vii) benzoylchloride, 1,2-DCE, pyridine, DMAP; (viii) TsOH, MeOH, H_2O, MeCN; (ix) TBDPS-Cl, imidazole, 1,2-DCE; (x) TMS-allyl, TMS-OTf, DCM.

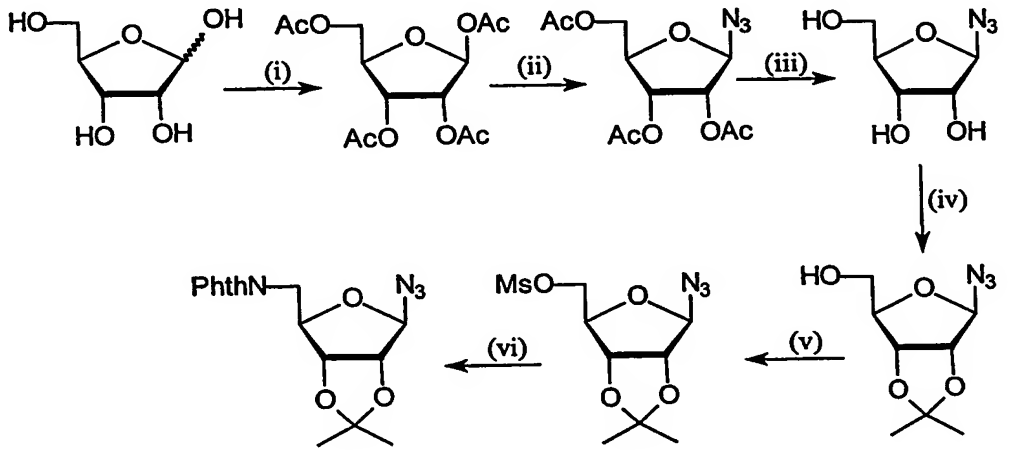
Example 15: Synthesis of a Range of C-Glycosides



*Ramburg-Backlund rearrangement of phthalimido thioglycosides **I** to give an exo methylene compound **II**. The products can them be converted to a variety of C-glycosides which can be further elaborated to building blocks as exemplified by **28**. The reaction pathway can furnish C-glycosides with a large number of alkyl or aromatic side-chains at the anomeric position. *Conditions*: (i) Oxone, (ii) KOH, CCl_4, (iii) BH_3, HOOH, H_2/Pd; (iv) H_2Pd; (v) ArX, Pd(0), H_2/Pd; (vi) AcSH, AIBN, H_2/Pd; (vii) (a) KOH, (b) TfN_3, RT, CH_2Cl_2, MeOH,

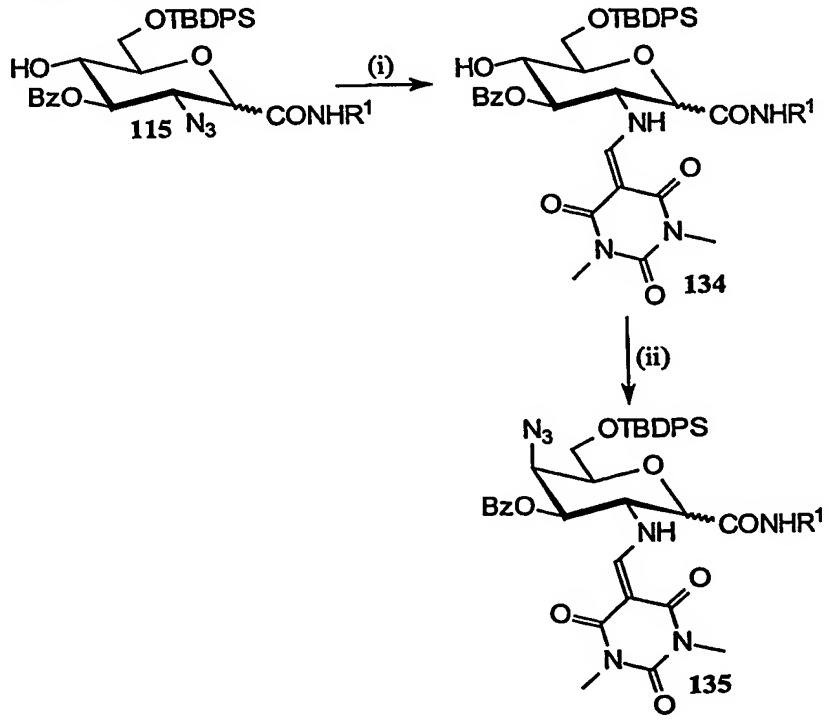
H_2O/cat. $CuSO_4$, 90%; (viii) Δ Δ-dimethoxytoluene, TsOH, MeCN/MeOH; (ix) BzCl, pyridine, (x) MeOH/MeCN/H_2O, TsOH; (xi) TBDPS-Cl, pyridine.

Example 16: Synthesis of a Furano Derivative



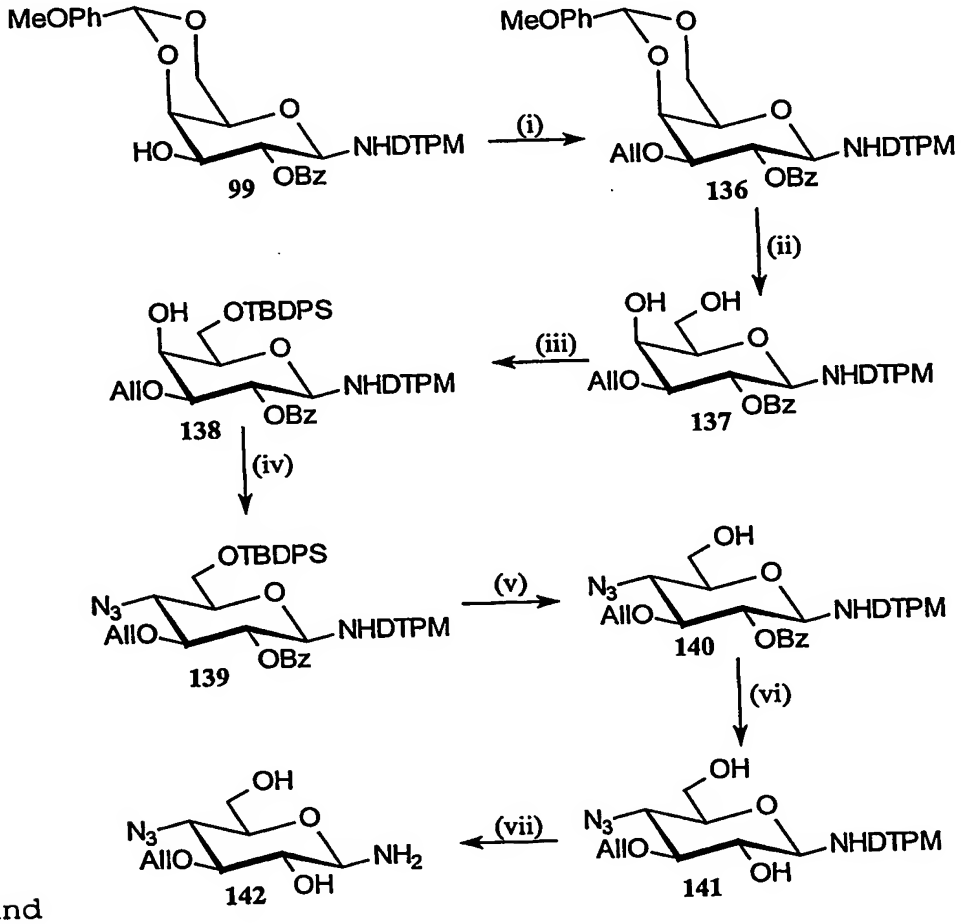
Conditions: (i) Ac_2O, NaOAc (ii) TMS-N_3, TMS-OTf, DCM; (iii) NaOMe/MeOH; (iv) 2,2-dimethoxypropane, TsOH, MeCN; (v) MsCl, pyridine; (vi) potassium phthalimide, DMF.

Example 17: Synthesis of a C-Glycoside as a 4-Deoxy-4-Azido Derivative



Conditions: (i) (a) DTT, (b) DTPM reagent; (ii) (a) Tf_2O, pyridine, DCM, (b) NaN_3, DMF.

Example 18: Synthesis of a Protected Glycosylamine Derivatised as a 4-Deoxy-4-Azido



Compound

Conditions: Allyl chloride, (ii) TsOH, MeOH/MeCN,H_2O; (iii) TBDPS-Cl, imidazole, 1,2-DCE; (iv) Tf_2O, pyridine, DCM, (b) NaN_3, DMF; (v) TBAF/THF; (vi) NaOMe/MeOH; (vii) hydrazine hydrate.

It will be apparent that the removal of either the silyl group, the benzoyl group or the allyl ether can be achieved in any order and the free hydroxyls thus formed may be alkylated with a range of X substituents. Additionally, the azide group may be reduced with for example dithiothreitol to provide a free

amine which can be reductively aminated with an aldehyde or acylated. The DTPM group may be removed with ammonia solution to provide a free amine which may be similarly derivatised. Compound 139 thus provides a scaffold for a wide variety of substitituons.

It should be appreciated that various other changes and modifications can be made to the invention without departing from the spirit and scope of the invention.

Dated this 28th day of March 2002

Alchemia Pty Ltd

By their Patent Attorneys

CULLEN & CO.

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